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INSTITUTION: THE ARMY MEDICAL RESEARCH UNIT OF THE UNIVERSITY
OF CHICAGO (STATEVILLE PENITENTIARY)

SUBJECT: STUDIES ON CHEMOTHERAPY OF VIVAX MALARIA, FALCIPARUM
MALARIA, AND PRIMAQUINE HEMOLYSIS

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Since the last interim report was submitted several strains of chloroquine-resistant P. falciparum have been investigated at Stateville on inmate volunteers. One strain of P. falciparum which originated in Thailand has been found resistant to all modern synthetic antimalarial drugs except quinine. It is resistant to the new depot antimalarial drug developed by Parke-Davis which will protect against the Chesson strain of vivax for six months to one year. Two more strains of falciparum malaria which have proved chloroquine-resistant in American military personnel are stored in deep freeze but have not been studied.

A strain of P. falciparum obtained from a Marine, Captain Snell, who was flown from South Viet Nam to Great Lakes Naval Hospital, has been studied in him and also in inmate volunteers to whom this strain was transmitted. The Snell strain of P. falciparum from South Viet Nam is resistant to all drugs except pyrimethamine and quinine. The doses of quinine that are necessary to cure this strain appear to be larger than is usually the case in falciparum infections. The Parke-Davis depot drug, C1-501, does not protect against the South Viet Nam strain.

A new potential antimalarial drug obtained from the Cancer Chemotherapy Program, which has been studied extensively in malignancies in humans, has also received therapeutic trial. This compound

is of interest because its action is known. It blocks the incorporation of valine into protein modities. Previous to therapeutic trial at Stateville this compound was studied in P. berghei infections in mice by Dr. Ralph Jones, Jr. and his group at the University of Miami. It was effective in berghei infections. When tested in volunteers at Stateville Penitentiary it could be demonstrated that the compound had partial effect in vivax malaria, but when given intravenously its toxicity was too great to warrant extensive testing. Toxicity consisted of a marked fall in blood pressure in one of the two patients studied. It would be worthwhile to study the effectiveness of similar compounds that could be given by mouth.

The hypothesis that primaquine sensitivity may be beneficial to the individual who has the characteristic enzyme deficiency in his blood (G-6-PD deficiency) is being tested. Preliminary results indicate that in all probability the enzyme deficiency does modify the severity of falciparum malaria, thus rendering individuals who possess this genetically transmitted characteristic at a biological advantage. Additional studies must be performed before final interpretations can be made, but thus far it appears that this enzyme deficiency is an example of balanced polymorphism.

Several additional biochemical characterizations have been

made of the red blood cells of individuals who lack G-6-PD. These studies concern the glyoxalase, adenine triphosphate and hexokinase of the cells. These enzymes do not appear to be involved in the initial stages of the hemolytic processes when drugs are administered to sensitive individuals. Likewise, the enzyme GA-3-PD does not change during primaquine administration and, therefore, is probably not directly involved in the mechanism of hemolysis.

Several genetic studies in heterozygous females who are primaquine sensitive are in progress but results were not available at the time the contract closed on 31 March 1963.

PUBLICATIONS

Alving, A.S., Powell, R.D., Brewer, G.J., and Arnold, J.D.:

**Malaria, 8-Aminoquinolines and Haemolysis. Biol. Council
Symp. on Drugs, Parasites and Hosts, 1962, pp. 83-97.
(no reprints available)**

Brewer, G.J., Powell, R.D. (by invitation) and Alving, A.S.: Studies

**on the Mechanism of the Primaquine-type Hemolysis:
Erythrocyte ATP Content and Hexokinase Activity. J. Lab. &
Clin. Med., November 1962., vol. 60, no. 5, (abstract)**

ABSTRACT

(Final Scientific Report)

1. **University of Chicago - Army Medical Research Unit, Stateville Penitentiary, Joliet, Illinois**
2. **Annual Progress Report: Studies on Chemotherapy of Vivax Malaria and Primaquine Hemolysis, by Alf S. Alving, George J. Brewer, and Alvin R. Tarlov**
3. **Dr. Alf S. Alving, Principal Investigator**
4. **Report: 4 Pages long including abstract**
5. **Contract number: DA-49-007-MD-566, Army Medical Research #14**
6. **Supported by: U. S. Army Medical Research and Development Command, Department of the Army, Washington 25, D. C.**

Since the last interim report of investigations at the University of Chicago-Stateville Medical Research Unit the therapeutic response of several strains of P. falciparum from Southeast Asia have been studied. One strain obtained from Malaya, one from Thailand and one from South Viet Nam have proved resistant to chloroquine. They are all sensitive to quinine. The Thailand and Viet Nam strains are resistant to the Parke-Davis depot drug C1-501.

Investigations of drugs developed on the Cancer Chemotherapy Program and tested in berghei infections of mice by Dr. Ralph Jones, Jr. of Miami have been initiated at Stateville Penitentiary in volunteers infected with Chesson vivax malaria.

Genetic and biochemical studies of primaquine sensitivity (G-6-PD deficiency) have continued.